INTRODUCTION

The etiology of infertility is diverse. Although the majority of couples will be found to have an identifiable male or a female factor explaining their inability to conceive, 10–25% will be labeled as having 'unexplained infertility'. Within this cohort of patients there is a spectrum of disorders ranging from those patients with a reduced fecundity that will conceive with time to those in whom conception is very unlikely with current medical practice. From the female perspective subfertility may reflect a diminished ovarian reserve, a disorder of oogenesis or suboptimal endometrial receptivity ***(Hull et al., 1985).***

Phosphodiesterase (PDE) is a family of isoenzymes that hydrolyse cAMP and cGMP. Specific inhibitors of PDE subtypes have been identified that can augment the effects of cyclic nucleotides on target tissues, such as human spermatozoa ***(Fisch et al., 1998).*** Sildenafil citrate (Viagra) is a newly developed, type 5-specific PDE inhibitor that prevents the breakdown of cGMP and potentiates the effects of NO on vascular smooth muscle. Since its introduction in 1997, sildenafil has been used with great success in the treatment of male erectile dysfunction ***(Boolell et al., 1996).***

Sildenafil citrate was the first PDE-5 inhibitor approved by the United States Food and Drug Administration (FDA). The mechanism of action for the PDE-5 inhibitors involves increased tissue levels of cGMP, which causes smooth muscle

relaxation and vasodilation. The clinical studies suggest some very promising new applications of PDE-5 inhibitors, far beyond their urological scope ***(Arch et al., 2006).***

The importance of endometrial appearance as a predictor of outcome in patients undergoing induction of ovulation is well established. However, treatment with oestrogens alone does not appear to improve pregnancy rates significantly in patients with poor endometrial response. NO is recognized as a mediator of vascular smooth muscle dilatation in many areas of the body. NTG has long been used for its vasodilatory properties in the treatment of angina, as well as obstetrically, to achieve tocolysis and uterine relaxation. We have used NTG successfully to improve uterine artery blood flow and endometrial lining in IVF patients with a previous poor response. However, we experienced a high rate of side-effects, including hypotension and headaches. The use of intravaginal sildenafil suppositories made it possible to decrease the incidence of these side effects by delivering medication in close proximity to the target organ ***(Gonen and Casper, 1993).***

AIM OF THE WORK

To compare effect of oral sildenafil citrate 25 mg versus placebo tablet on pregnancy rate as primary outcome and the endometrial thickness and number of follicles as secondary outcome in women undergoing induction of ovulation.

INFERTILITY

Definition:

Infertility is defined as inability to establish pregnancy within a specific period of time; usually one year with unprotected intercourse ***(Ashok et al., 2000).*** In contrast to sterility, infertility is not an irreversible state. The term primary infertility is applied to the female who has never achieved a pregnancy; secondary infertility implies that at least one previous conception has taken place ***(Rein et al., 1999).***

Possible Etiologies:

These include:

1- Ovarian and endocrine factors.

2- Uterine factor.

3- Peritoneal factors.

4- Tubal factor.

5- Immune factors

6- Cervical factors

7- Male factor.

8- Embryological factors

9- Infection.

(Mishell et al., 1997)

While the factors and problems listed above can be identified by medical tests, a wide variety of other factors may be affecting fertility. As example, people with some genetic disorders (such as cystic fibrosis) are more likely to experience fertility problems. Several lifestyle factors, general health and chemical exposure issues can affect the ability to conceive particularly smoking, obesity and stress ***(Cahill et al., 2002).***

Evaluation of Infertile Couple:

The approach in the infertile couple should begin with a detailed medical, sexual and social history followed by physical examination of both partners. The sequence of investigation should be ordered so that the simple, least invasive and most productive tests are compl4- Tubal factor ***(Thompson et al., 1997)***.

- ***Evaluation of male infertility:***

Diagnostic test for male factors:

1. ***Semen analysis:***

- Sperm variables (density, motility, morphology).
- Seminal fluid variables (volume, PH).
- Other cells or bacteria (pus cells, round cells).

2. Sperm cell properties:

- Movement characteristics (video micrography).
- Membrane integrity (hyper 'osmotic swelling').

- Biochemical properties (acrosin concentration).

3. Sperm cell function:

- In vivo mucus penetration (postcoital test).
- In vitro mucus penetration.
- Fertilizing capacity (sperm-hamster egg penetration).

Table (1): Semen analysis: Reference values on at least two occasions.

Ejaculate volume	1.5-5.0 ml
pH	>7.2
Sperm concentration	> 20 million/ml
Total sperm number	> 40 million/ejaculate
Percent motility	> 50%
Forward progression	> 2 (scale 0-4)
Normal morphology	> 50% normal*
	> 30% normal**
	> 14% normal***
Sperm agglutination	< 2 (scale 0-3)
Viscosity	< 3 (scale 0-4)

* World Health Organization, 1987.
** World Health Organization, 1992.
***Kruger (Tygerberg) Strict Criteria, World Health Organization, 1999.

- ***Evaluation of female infertility:***

Medical History:

Important points in it:

1. Sexual dysfunction: Dyspareunia and Vaginismus, coital frequency, orgasm.
2. Endocrine: Menstrual pattern, hirsutism, Acne, oily skin, weight changes, eating disorders, galactorrhea and thyroid symptoms.
3. Uterine and tubal, pelvic or abdominal surgery.
4. Pelvic infection, pelvic pain, dysmenorrhea or sexually transmitted diseases.
5. Cervical factor: Mucous secretion, conization, cautarization.
6. Ovulation cascade: Dysmenorrhea.
7. Previous obstetric history: Pregnancy loss, Puerperal sepsis.
8. Contraception: Hormonal, intrauterine contraceptive device.

Surgical history:

The surgical history should focus on the pelvis because any surgery on the reproductive organs, bowel, or bladder can cause pelvic inflammation, adhesions, and tubal damage.

Physical examination:

Once the history is taken the patient should be examined. This examination should cover all the systems with particular attention to the reproductive system. The height and weight are recorded and the body mass index (Kg/m^2) is calculated. Breasts are checked for the development and secondary sexual characteristics' are noted. Abdominal palpation and a pelvic examination should check for the gross abnormality of the pelvic organs.

Methodology of basic investigations of the female factors:

(1) Ovulation detection:

Direct methods involve seeing follicle growth and rupture by laparoscopy or high-resolution transvaginal ultrasound examination. Laparoscopy is invasive and ultrasound monitoring requires inconvenient daily monitoring of follicular growth. Both are very expensive. Ultrasound examination was critical to differential diagnosis between ovulation and luteinized unruptured follicle syndrome. The indirect methods of predicting ovulation rely on measurement of LH or estrogen in blood, urine, or saliva, ascertainment of basal body temperature (BBT) nadir, or analysis of cervical mucus. Methods used to detect the LH surge in urine have a higher incidence of false-negative results than radioimmunoassay

applied to serum samples, but repeated measurement of circulating LH is invasive and expensive. Indirect methods used to confirm ovulation are the measurement of serum progesterone, related changes in BBT, or endometrial histology. Serum progesterone- has at least two drawbacks, the cutoff serum levels of ovulatory progesterone are not well defined and the *vi*ability in cycle length dictates the need of two or three samples to avoid underestimation of ovulation frequency. Basal body temperature is an easy, inexpensive, and self-administered method, but can be affected by many factors other than hormonal changes. Endometrial biopsy and dating, besides being invasive, have no correlation with impaired fertility, and is used less ***(Eliade et al., 2001).***

(2) Methodology of investigations of tubal, uterine and pelvic factors:

- ***Ultrasound:*** Transvaginal ultrasound should be part of the routine evaluation of infertile patient. It allows a precise evaluation of the position of the uterus within the pelvis and provides more information about its size and irregularities. It also helps in the early detection of uterine fibroid, endometrial polyp, ovarian cysts, adenexal masses and endometriomas ***(Jairo, 2004)***.
- ***Hysterosalpingography:*** Hysterosalpingography is a radiographic examination of endocervical canal, uterine cavity and Fallopian tube with the use of a radiographic contrast medium. This method is an integral part of

gynecological examination and its value has not been underestimated in the modern gynecological practice ***(Ganovi et al., 2002).***

- ***Laparoscopy:*** The gold standard for diagnosing tubal and peritoneal disease is laparoscope. It allows visualization of all the pelvic organs and permits detection of peritubal and periovarian adhesions, and endometriosis**.** The enhanced optics and magnification and the improved instrumentation now permit surgical treatment of tubal obstruction, pelvic adhesions and endometriosis at the time of diagnosis ***(Promecene et al., 2002).***
- ***Falloposcopy:*** Falloposcopy is a more complicated and more expensive procedure involving the passage of an extremely fine flexible fibreoptic device from the uterine cavity distally to the fimbriae. In order to pass the device a balloon surrounding the endoscope is inflated along the tube and the scope advanced, bit by bit, to minimize tubal damage ***(McClure et al., 1997).***
- ***Hystroscopy:*** Hystroscopy is a method of direct visualization of the endometrial cavity. The procedure can be performed in the physician's office using local anesthesia (paracervical block) ***(Jairo, 2004).***
- ***Hysterosonosalpingography:*** It is a contrast ultrasound method which is used in the assessment of the uterine cavity and fallopian tubes. It is useful in making decisions

regarding, further procedures for the diagnosis and treatment of infertility ***(Radic et al., 2005).***

(3) Methodology of investigations of cervical factor:

• ***The postcoital test:*** The postcoital test is the microscopic examination of the cervical mucus, performed shortly before expected ovulation and within 8 to 12 hours after intercourse, to identify the presence of motile sperm in the mucus ***(Oei, 1998).***

THE MENSTRUAL CYCLE&OVULATION

Normal menstrual cycle is divided into three phases; follicular, ovulatory and luteal phases. Each phase is associated with changes in pituitary and ovarian hormones which correlates with the morphologic changes that occurs in reproductive organs and the auto-paracrine events in the ovary ***(Hayflick et al., 2005).***

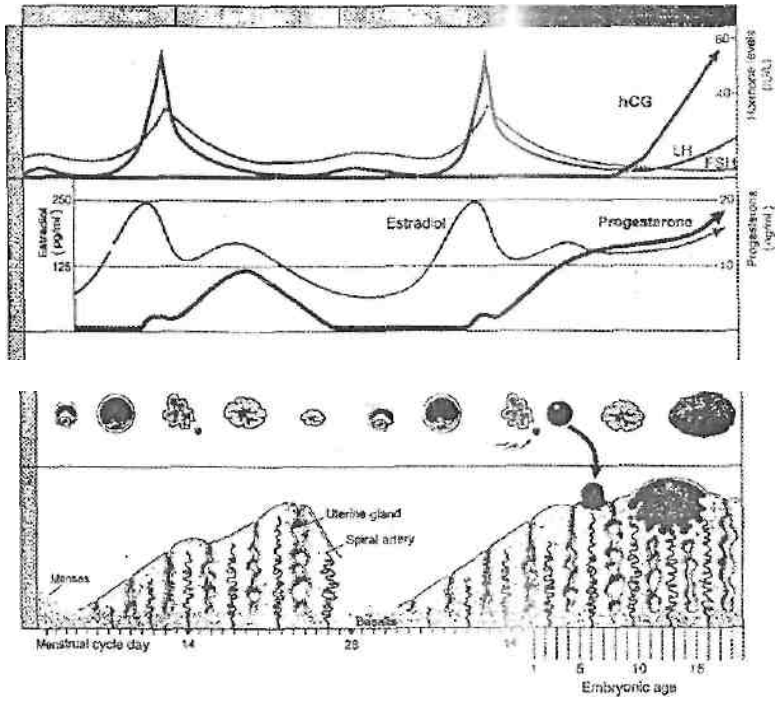

Fig (1): Cyclic changes in the blood levels of sex hormones and their biological effects ***(David, 2007).***

The Three major organs that regulate human reproduction are the hypothalamus, the pituitary and the ovary. The central nervous system - pituitary complex determined and directed the chronology of developmental events within a reproductive ovary. However the menstrual cycle is controlled by the sex-steroids and peptides produced within the follicle destined to ovulate ***(Dixons, 2001).***

The direction of the blood flow in the hyperphysical portal circulation is from the brain to the pituitary. There is also retrograde flow so that pituitary hormones can be delivered to hypothalamus, creating that opportunity for pituitary feedback on the hypothalamus ***(King et al., 2005).***

A. Hypothalamus

Hypothalamus is the part of diencephalons at the base of the brain just above the junction of the optic nerves, which forms the floor of the third ventricle and part of its lateral walls ***(Sherwood et al., 2005).***

GnRH secretion:

GnRH is a decapeptide derived from a large precursor molecule (12 amino acids) the biological activity of GnRH is very short, with a half-life of 4-6 minute and secreted in a pulsatile pattern, with 60to 90-minute intervals during the follicular phase and 4 hours intervals during the mid-luteal phase. Its secreting cells are neurons of the arcute nucleus

whose axons traverse the median eminence of the mediobasal hypothalamus when it is synthesized, stored and transported to the portal capillaries via the neuronal axons ***(Adam, 2002).***

The molecule of GnRH binds specifically to a receptor on membrane of gonadotropic cells of the pituitary gland leading to synthesis and regulation of follicle stimulating hormone (FSH) and leutenizing hormone (LH) **(Fig. 2)** ***(Roberts et al., 2005).***

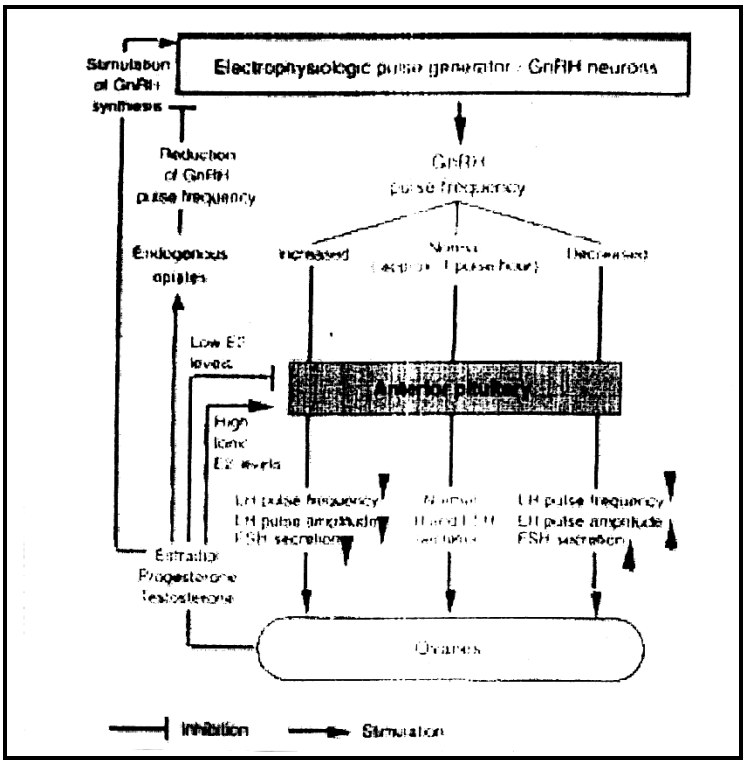

Fig (2): GnRH pulse frequency: effect on LH & FSH secretion. The secretion of LH & FSH is modulated (usually suppressed) by steroids, and the action of GnRH alone has virtually no effect on the pituitary in vivo. The postmenopausal increase in LH & FSH is due to the lack of steroid suppression ***(Rabe et al., 2002).***

B. Pituitary

The pituitary gland is located in the sella tursica in relation to optic chiasma, and formed of anterior and posterior loops The gonadotropic cells which present in the anterior pituitary is responsible for synthesis of gonadotropins FSH &LH ***(Melis et al., 1998).***

In the menstrual cycle, prime role of adenohypophysis is to allocate gonadotropins FSH & LH. GnRH controls and regulates the synthesis, storage and secretion of these hormones. Because GnRH is secreted in a pulsatile manner, FSH & LH respond accordingly with pulsatile mechanism. But, pituitary suppression occurs with giving GnRH agonist in non-pulsatile mechanism which is commonly used during IVF treatment ***(Jarvela et al., 2003).***

Control of the reproductive cycles depends on constant release of GnRH. This function depends on the complex and coordinated interrelationships among these releasing hormones, other neurohormones, the pituitary gonadotropins and the gonadal steroids. The interplay among this substance is governed by feedback effects both stimulatory and inhibitory. The long feedback loop refers to the feedback effects of circulating levels of target gland hormones, and this occurs both in the hypothalamus and pituitary, positive feedback is illustrated by the midcycle effect of estradiol (E2) and progesterone on the LH, and negative feedback refers to the